REMARKS

After entry of the amendments above, claims 33-48, 65-96 and 113-272 will be pending. No new matter is added by the amendments to the claims. Applicants respectfully request reconsideration and withdrawal of the outstanding rejections in view of the following remarks.

1. Formal Matters

On page 2 of Paper No. 25, paragraph C, the Examiner indicated that "since Statutory Declarations are not proper subject matter for an IDS, Applicants have not submitted a Form PTO-1449" for the Statutory Declarations submitted in the Information Disclosure Statements mailed April 18, 2002.

Applicants wish to thank Examiner Landsman for clarifying the significance of the Examiner's comments in paragraph C in a telephonic interview with Applicants' representative, Melissa Pytel, on January 29, 2003. Because Applicants wish to have the Statutory Declarations considered by the Examiner and marked in the record as such, Applicants provide herewith an Information Disclosure Statement and Form SB/08, listing the Statutory Declarations.

As discussed in the telephonic interview with Examiner Landsman, Statutory Declarations are proper material for an Information Disclosure Statement. 37 C.F.R. §1.56(a) states that an applicant has a duty to disclose to the Patent Office all information that is material to patentability. 37 C.F.R. §1.98(a)(1) states that an information disclosure statement shall include a list and a legible copy "of all patents, publications, applications, *or other information* submitted for consideration by the Office." (Emphasis added.) Applicants submit that the Statutory Declarations constitute "other information" under 37 C.F.R. §1.98 that may include information that is material to the patentability of the instant application and are therefore contemplated by 37 C.F.R. §1.56(a) as information to be included in an IDS. Applicants therefore respectfully request that the Statutory Declarations listed on the form SB/08 be initialed as considered by the Examiner.

2. Information Disclosure Statement

The Examiner also indicated that reference FA, an International Search Report submitted in the response mailed March 12, 2002, has been lined through because "an international search report is not a proper reference for an IDS." (Paper No. 25, page 3).

Applicants respectfully submit that the International Search Report was properly submitted to show the characterization of the references cited by the Examiner during prosecution of the corresponding PCT application. As discussed in connection with the Statutory Declarations above, Applicants submit that the International Search Report constitutes "other information" under 37 C.F.R. §1.98 that is material to patentability. However, since all of the references cited in the Search Report were listed on the form 1449 and initialed as considered by the Examiner, the issue is moot.

3. Double Patenting Rejections

Double Patenting Rejection

The Examiner rejected claims 33, 34, 49, 50, 65, 66, 81, 82, 97, 98, 113, 114, 129, 130, 145, 146, 161, 162, 177, 178, 193, 194, 209, 210, 225, 226, 241, 242, 257 and 258 under the judicially created doctrine of double patenting over claims 1-5, 7-11 and 14 of US Patent No. 5,932,540. Applicants respectfully submit that the Terminal Disclaimer submitted herewith obviates this rejection.

Provisional Double Patenting Rejections

The Examiner *provisionally* rejected claims 33, 34, 49, 50, 65, 66, 81, 82, 97, 98, 113, 114, 129, 130, 145, 146, 161, 162, 177, 178, 193, 194, 209, 210, 225, 226, 241, 242, 257 and 258 under the judicially created doctrine of obviousness-type double patenting over the claimed invention in the following copending U.S. Applications: 09/214,442, 09/935,726, 08/465,968, and 09/623,725. Claims 33-272 were *provisionally* rejected over claims 22-89 of copending U.S. Application No. 09/107,997.

Applicants acknowledge the provisional rejection. Upon receipt of a notice of allowance in this or in one of the above-referenced applications, Applicants will file an appropriate disclaimer in the remaining application, to the extent that such a disclaimer is necessary, or will cancel any conflicting claims that remain pending.

Possible Provisional Double Patenting Rejections

The Examiner also indicated the claims of the instant application *may* receive a provisional rejection for double patenting in a subsequent Office Action over U.S. Application Nos. 10/060,523, 10/084,488, and 10/127,551. At the time the present Office Action was mailed, the applications were either not available to the Examiner or no election had been made. Applicants thank the Examiner for the notification that a future provisional rejection may be issued for double patenting over the listed applications.

4. Enablement Rejections Under 35 U.S.C. §112, First Paragraph

A. ATCC Deposits

The Examiner has maintained the rejection of claims 97-192 under 35 U.S.C. §112, first paragraph, as containing subject matter which is not enabled because there is no indication in the specification as to the public availability of the deposited nucleic acid molecules contained in ATCC Deposit Nos. 75698 and 97149 (Paper No. 25, page 6).

In response, Applicants' representative hereby gives the following assurance by signature below:

Human Genome Sciences, Inc., the assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. This deposit comprises cDNA sequences encoding Vascular Endothelial Growth Factor-2. The deposits were given ATCC Accession Numbers 75698 and 97149 and were made on March 4, 1994 and May 12, 1995, respectively.

In accordance with M.P.E.P. §2410.01 and 37 C.F.R. §1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Numbers 75698 and 97149 have been removed due to the issuance of U.S. patents on priority applications. A copy of the ATCC Deposit Receipt for Accession Numbers 75698 and 97149 are enclosed herewith as **Attachments A and B**, respectively.

In light of the above statement regarding availability of the deposited material, Applicants submit that the Examiner's rejection of claims 97-192 under 35 U.S.C. §112,

first paragraph, is obviated and reconsideration and withdrawal of the rejection is respectfully requested.

B. 90% identity

The Examiner has maintained the rejection of claims 33-272 under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Examiner asserts that the specification does not provide enablement for "any protein which is at least 90% identical to the mature or proprotein form of SEQ ID NO:2 or 4, which comprises at least 30 contiguous amino acids of the mature or proprotein form of SEQ ID NO:2 or 4, or which are identical to only a portion of SEQ ID NO:2 (i.e. amino acid residues 71-396, 47-396 and 24-396)." (Paper No. 25, page 6). Applicants respectfully traverse.

As a preliminary note, Applicants respectfully request clarification of the Examiner's statement regarding proteins that comprise "at least 30 contiguous amino acids of the mature or proprotein form of SEQ ID NO:2 or 4" (Paper No. 25, page 6, line 30) and "at least 30 contiguous amino acids of SEQ ID NO:2, 4 (or to ATCC No. 75698 and 97149)" (Paper No. 25, page 7, lines 11-12). None of the pending claims recite this limitation. Applicants therefore request withdrawal or clarification of this rejection.

In the Office Action, the Examiner states that "the fact that a protein, or protein fragment, binds an antibody does not demonstrate that the protein is functional, and does not allow the artisan to make a functional protein." (Paper No. 25, page 7). The Examiner also asserts that "Applicants provide no guidance or working examples of how to use said peptides... which retain the claimed biological function." *Id.* Although Applicants disagree with the Examiner's statement, and maintain that the claims were enabled as pending, in the interest of advancing prosecution, the claims have been amended to recite "wherein said isolated protein has endothelial cell proliferative activity." Because the claims now recite a specific biological function (*i.e.*, endothelial cell proliferative activity), Applicants respectfully submit that the Examiner's concerns with respect to whether or not the protein is functional and whether or not one of skill in the art would know how to use such a protein have been obviated.

The Examiner also states that "Applicants have not provided any guidance or working examples as to which amino acid residues are required in order to produce a functional VEGF-2 protein." (Paper No. 25, page 7). Applicants respectfully disagree.

Contrary to the Examiner's assertion, the specification provides ample guidance as to which amino acid residues are required in order to produce a functional VEGF-2 protein. For example, the specification teaches that VEGF-2 is a member of the PDGF/VEGF family, which shares a conserved motif of eight cysteine residues (Specification, page 9, lines 5-14). FIG. 3 illustrates the amino acid homology between members of the PDGF/VEGF family and highlights the location of the eight conserved cysteine residues.

The specification clearly teaches the significance of the structural motif for the retention of VEGF-2 activity (Specification, page 9, lines 11-14 and lines 21-25; page 18, line 30 through page 19 line 2, and FIG. 3). The specification emphasizes that, in addition to the importance of conservation of the eight cysteine residues among the members of the PDGF/VEGF family, the signature consensus sequence for the PDGF/VEGF family, PXCVXXXRCXGCCN, is conserved in VEGF-2 (Specification, page 9, lines 11-15). In light of the teachings of the specification, one skilled in the art would reasonably expect that the conserved motif or signature consensus sequence should be maintained in VEGF-2 fragments in order to retain biological activity.

The specification also provides guidance to the skilled practitioner as to what amino acids can be altered while maintaining the desired activity. For example, Table 1, found on page 20 of the specification, lists conservative amino acid substitutions. At page 19, lines 5-6, the specification describes "substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids." Also, on page 18, lines 14-18, the specification references Bowie, et al., which describes phenotypically silent amino acid changes. At page 18, line 19 to page 19, line 2, the specification teaches that VEGF-2 fragments, derivatives, or analogs may be:

> (i) one in which one or more of the amino acid residues are substituted with a conserved or nonconserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code; or (ii) one in which one or more of the amino acid residues includes a substituent group; or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol); or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence; or (v) one in which comprises fewer amino acid residues shown in SEQ ID NOS:2 or 4, and retains the

conserved motif and yet still retains activity characteristics of the VEGF family of polypeptides.

Additionally, Applicants submit that at the time the instant specification was filed, it was common in the art to make changes to proteins through substitutions, deletions, insertions, and/or additions. This is supported by references in the specification to publications, such as Bowie, et al. (Specification, page 18, lines 16-17) and Ostade, et al. (Specification, page 19, line 15), which demonstrate the skill in the art at the time the application was filed.

The specification also enables the skilled artisan to determine whether a protein falls within the scope of the claims. Specifically, the specification teaches assays and methods useful for determining whether a polypeptide retains biological activity (*See, for example,* specification, page 16, lines 18-20, and Examples 4 and 5). Thus, one skilled in the art could readily determine whether a polypeptide fragment retains the claimed activity using assays and methods taught in the specification.

The fact that some experimentation may be necessary to determine whether a polypeptide fragment retains the claimed activity does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also, Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1376, 1384 (Fed. Cir. 1986). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." M.P.E.P. § 2164.06 (*citing, In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Furthermore, under 35 U.S.C. § 112, an inventor is not required to disclose "a test of every species encompassed by their claims," even in an unpredictable art. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (emphasis in original). Finally, enablement is not precluded even if some embodiments of the claimed invention are inoperative. Indeed, the M.P.E.P. states that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." *See*, M.P.E.P. § 2164.08(b).

Applicants respectfully submit that screening molecules for a desired activity is well within the ability of one of skill in the art. Therefore, taking the teachings in the

specification regarding conservative substitutions and the significance of the conserved motif, as well as the methods disclosed for determine whether a particular polypeptide has the claimed activity, one skilled in the art could easily make the claimed polypeptides without undue experimentation.

Although Applicants maintain that the claims were enabled as pending, in the interest of furthering prosecution, claims 161 and 177 have been amended to recite "wherein said isolated protein comprises SEQ ID NO:8" in which SEQ ID NO:8 refers to the 14 amino acid consensus sequence that is "the signature for the PGDF/VEGF family" (*See,* Specification, page 9, lines 11-14).

For the reasons discussed above, Applicants submit that the specification teaches one skilled in the art to make and use any and all polypeptides encompassed by the claims without undue experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

5. Written Description Rejections Under 35 U.S.C. §112, First Paragraph

A. 90% identity

The Examiner has maintained the rejection of claims 33-272 under 35 U.S.C. §112, first paragraph as lacking written description "with regard to any isolated protein which is at least 90% identical to the mature or proprotein form of SEQ ID NO:2 or 4, which comprises at least 30 contiguous amino acids of the mature or proprotein form of SEQ ID NO:2 or 4, or which are 90% identical to only a portion of SEQ ID NO:2." (Paper No. 25, page 7). Specifically, the Examiner asserts that the specification and claims do not indicate what distinguishing attributes are shared by the members of this genus other than SEQ ID NO:2 and 4. Applicants respectfully disagree and traverse.

Again, Applicants note the Examiner's statement regarding proteins that comprise "at least 30 contiguous amino acids of the mature or proprotein form of SEQ ID NO:2 or 4" (Paper No. 25, page 7). Since none of the pending claims recite this limitation, Applicants request withdrawal or clarification of this rejection.

A patent specification, in order to satisfy the written description requirement, must describe the claimed invention in sufficient detail to allow a skilled artisan to reasonably conclude that the inventor had possession of the claimed invention at the time the application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

Applicants submit that the instant specification provides a sufficient description of the claimed invention such that a skilled artisan would reasonably conclude that the inventors had possession of the invention at the time the application was filed. The specification describes distinguishing attributes that are shared by members of the genus. For example, the specification describes a conserved functional motif of eight cysteine residues and the consensus sequence PXCVXXXRCXGCCN (SEQ ID NO:8), which is important in maintaining biological activity, such as endothelial cell proliferative activity (Specification, page 9, lines 11-14).

The specification also provides guidance to the skilled practitioner as to other amino acid modifications, such as conservative amino acid substitutions (Specification, Table 1, page 20) and phenotypically silent amino acid changes (Specification, page 18, lines 14-18) that can be made and while maintaining the recited biological activity. Furthermore, at the time the instant specification was filed, it was common in the art to make changes to proteins through substitutions, deletions, insertions, and/or additions.

Therefore, one of skill in the art, from reading the disclosure, could readily envision and identify by specific amino acid sequence the individual polypeptides that have an amino acid sequence at least 90% identical the mature or proprotein form of SEQ ID NO:2 or 4; ATCC Deposit Nos:97149 or 75698; and the specified fragments and have endothelial cell proliferative activity.

Although Applicants maintain that the claims are supported by an adequate written description as pending, in the interest of furthering prosecution, independent claims 33, 65, 81, 113, 129, 145, 161, 177, 193, 209, 225, 241 and 257 have been amended to recite that the isolated protein has endothelial cell proliferative activity. Furthermore, claims 161 and 177 have been amended to recite that the isolated protein comprises SEQ ID NO:8. Applicants therefore request withdrawal of this rejection.

B. Mature or Proprotein

The Examiner further rejected claims 33-64 and 97-128 as lacking written description because "the instant specification fails to describe that portion of a protein which is the 'mature' portion, or what constitutes a 'proprotein'." (Paper No.25, page 8). Applicants respectfully disagree and traverse.

In the specification, "proprotein" and "mature" portions of VEGF-2 are specifically described as follows:

> The present invention also includes polynucleotides, wherein the coding sequence for the mature polypeptide may be fused in the same reading frame to a polynucleotide which aids in expression and secretion of a polypeptide from a host cell, for example, a leader sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell. The polypeptide having a leader sequence is a preprotein and may have the leader sequence cleaved by the host cell to form the mature form of the polypeptide. The polynucleotides may also encode for a proprotein which is the mature protein plus additional 5' amino acid residues. A mature protein having a prosequence is a proprotein and is an inactive form of the protein. Once the prosequence is cleaved an active mature protein remains.

Specification, page 11, lines 11-21. Additional description of the "mature" and "proprotein" forms can be found at page 9, lines 5-8 and page 10, lines 4-17.

From the teachings in the specification, one skilled in the art could readily envision and identify polypeptides that fall within the recited "mature" and "proprotein" terminology. Applicants therefore submit that the specification provides adequate written description for the terms "mature" and "proprotein" sequences.

Furthermore, the M.P.E.P. states that by "disclosing in a patent application a device that *inherently* performs a function or has a property, operates according to a theory or has an advantage, a *patent application necessarily discloses* that function, theory or advantage, even though it says nothing explicit concerning it." M.P.E.P. § 2163.07(a).

Applicants submit that the mature portion of the protein is inherently disclosed in the patent application through its teachings. All of the information required for one of skill in the art to obtain the mature processed form of a polypeptide is found within the amino acid sequence of the precursor form of the polypeptide. The nucleotide sequence of the precursor form of VEGF-2 inherently contains all of the motifs required for the cell to process the protein to a mature form of VEGF-2. As demonstrated by the Declaration of Dr. Stuart Aaronson (the "Aaronson Declaration"), which was submitted in co-pending U.S. Patent Application Serial No. 08/107,997 and is appended hereto as **Attachment C**, the capacity of the VEGF-2 polypeptide to be expressed and proteolytically processed to the mature form of the protein is a natural and intrinsic property of that molecule. The

expression and proteolytic processing of the VEGF-2 polypeptide to the mature form of the protein is a result of the cell's recognition of the "signals" present in the amino acid sequence of the precursor form of the polypeptide. Thus, one of skill in the art, armed with the teaching of the specification would have all the information required to express and isolate a mature and biologically active form of VEGF-2.

The Examiner also contends that "the structure of a 'mature form of a polypeptide' cannot be predicted on the basis of the amino acid sequence of the entire protein since the protein may be proteolytically cleaved in vivo, as well as being differentially processed based on which in [sic] tissue the protein is expressed." (Paper No. 25, page 8). However, the Examiner fails to appreciate that the mature, processed form is an inherent property of the precursor form of VEGF-2, and its capacity to be processed is also an inherent, intrinsic property which does not vary. As demonstrated by the Aaronson Declaration, it is not unexpected that the processing of the precursor form may vary depending on the expression system used (See ¶12, of the Aaronson Declaration). However, it is unnecessary for the patent specification to specifically describe either the mechanics of processing or each of the resulting processed forms, as the processing is an automatic and natural event. Thus, other than provide the amino acid sequence of the precursor form, no other information is required for one of skill in the art to achieve the mature form, nor is more information required for one to recognize that the applicants were in possession of the claimed invention.

The function of the "written description" requirement of 35 U.S.C. 112, first paragraph, is to ensure that applicants had possession of the claimed subject matter, as of the filing date of application relied on. *In re Blaser*, 556 F.2d 534, 194 USPQ 122 (CCPA 1977). The inquiry into satisfaction of the written description requirement is factual and depends on the nature of the invention and the amount of knowledge imparted to those of skill in the art by the disclosure. *In re Wertheim*, 646 F.2d 527, 191 USPQ 90 (CCPA 1976). Satisfaction of the "written description" requirement does not require *in haec verba* antecedence in the originally filed application. *In re Lukach*, 440 F.2d 1263, 169 USPQ 795 (CCPA 1971). The written description requirement can be satisfied by showing that the disclosed subject matter, when given its 'necessary and only reasonable construction,' inherently (*i.e.*, necessarily) satisfies the limitation in question. *Staehelin v. Secher,* 24 USPQ2d, 1513, 1520 (Bd. Pat. Int'f. 1992) ("a specification need not describe

the exact details for preparing every species within the genus described"). In general, precedent establishes that although the applicant 'does not have to describe exactly the subject matter claimed, the description must clearly allow persons of skill in the art to recognize that [the applicant] invented what is claimed.' *In re Gosteli,* 872 F.2d 1008,1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Applicants invite the Examiner's attention to the Aaronson Declaration, submitted herewith as **Attachment C**, as evidence that one of ordinary skill in the art would recognize that the applicants were in possession of the claimed invention as of the March 8, 1994 filing date of the priority application serial no. 08/207,550 (*In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996)). As shown by the Aaronson Declaration, the precursor form of a polypeptide intrinsically contains the signals required to result in the processing to the mature form of the protein (See Aaronson Declaration at ¶¶13 to 17). As evidenced by ¶¶6 to 12 of Aaronson's Declaration, the 350 amino acid sequence of VEGF-2 contains all of the information and motifs required to allow the host cell to process the 350 amino acid sequence to the mature form of VEGF-2. The molecular weight of the mature form of VEGF-2 expressed and obtained by the cell is an inherent property that is the result of proteolytic processing of the precursor form of VEGF-2 (See Aaronson Declaration at ¶¶13 to 17). Indeed, as provided by the Aaronson Declaration, both the 350 amino acid form and the 419 amino acid form of VEGF-2 are identically processed to the mature form of VEGF-2, resulting in the secretion of polypeptides of identical molecular weights, as assessed by SDS PAGE.

To overcome a prima facie case of unpatentability under 35 U.S.C. §112, first paragraph, the applicants must show by evidence or argument that the invention as claimed is adequately described to one of ordinary skill in the art. *In re Alton* 76 F.3d 1168, 1175 (Fed. Cir. 1996). The Aaronson Declaration provides evidence that one of skill in the art would recognize that the mature form of VEGF-2 is adequately described by the instant application. If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claim is not explicitly described in the specification, then the adequate written description requirement is met. *In re Alton* 76 F.3d 1168, 1175 (Fed. Cir. 1996). The Federal Circuit has noted that the priority application need not use the identical words to describe the claimed invention, if it shows the subject matter claimed with an adequate

direction as to how to obtain it. *Kennecott v. Kyoura International, Inc.* 835 F.2d 1419. 1422, 5 USPQ 2d 1194, 1197 (Fed. Cir. 1987), *cert denied*, 486 U.S. 1008 (1988).

In this instance, the priority application and the instant application clearly describe the subject matter of the invention and also provide adequate direction as to how to obtain the mature form of VEGF-2. Furthermore, as evidenced by the Aaronson Declaration, one of ordinary skill in the art would recognize that the applicants were in possession of the claimed invention. Indeed, it is unnecessary for the specification to explicitly define by amino acid sequence, the beginning and end of the processed, mature form of VEGF-2 in order for one skilled in the art to recognize a "mature portion of a protein." The specification teaches the "mature portion" of VEGF-2 because the "mature portion" of VEGF-2 is naturally and inherently produced when expressed by a host cell.

Thus, the instant specification, and the specification of the priority application, contains sufficient information required of one of ordinary skill in the art to recognize that the applicants were in possession of the invention as claimed. Hence, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants believe they have fully addressed the Examiner's concerns and that this application is now in condition for allowance. An early notice to that effect is urged. A request is made to the Examiner to call the undersigned at the phone number provided below if any further action by Applicants would expedite allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should be charged to our Deposit Account.

Dated: February 4, 2003

Respectfully submitted,

By _____
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Enclosures
MMW/MJP/AKR/lcc

Docket No.: PF112P2D2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Hu et al.

Application No.: 09/257,272-Conf. #1980

Filed: February 25, 1999

For: Vascular Endothelial Growth Factor-2

Docket No.: PF112P2D2

Group Art Unit: 1647

Examiner: R. Landsman

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please show the amendments to the claims as follows:

33. **(Amended)** An isolated protein comprising an amino acid sequence at least 90% identical to a mature form of a polypeptide of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

49-64. **(Canceled)**

65. **(Amended)** An isolated protein comprising an amino acid sequence at least 90% identical to a proprotein form of a polypeptide of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds to an antibody that specifically binds to SEQ ID NO:2~~.

81. **(Amended)** An isolated protein comprising an amino acid sequence at least 90% identical to a proprotein form of a polypeptide of SEQ ID NO:4, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds to an antibody that specifically binds to SEQ ID NO:4~~.

97-112. **(Canceled)**

113. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a mature form of a polypeptide encoded by the cDNA contained in ATCC Deposit No. 97149, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

129. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a proprotein form of a polypeptide encoded by the cDNA contained in ATCC Deposit No. 75698, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds tan antibody that specifically binds to SEQ ID NO:4~~.

145. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a proprotein form of a polypeptide encoded by the cDNA contained in ATCC Deposit No. 97149, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

161. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide encoded by the cDNA contained in ATCC Deposit No. 75698, wherein said isolated protein comprises SEQ ID NO:8 and has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:4~~.

177. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide encoded by the cDNA contained in ATCC Deposit No. 97149, wherein said isolated protein comprises SEQ ID NO:8 and has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

193. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide comprising amino acids 71 to 396 of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

209. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide comprising amino acids 47 to 396 of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

225. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide comprising amino acids 24 to 396 of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

241. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide comprising amino acids 1 to 396 of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.

257. **(Amended)** An isolated protein comprising an amino acid sequence that is at least 90% identical to a polypeptide comprising amino acids -23 to 396 of SEQ ID NO:2, wherein said isolated protein has endothelial cell proliferative activity ~~specifically binds an antibody that specifically binds to SEQ ID NO:2~~.